UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Wednesday, January 27, 2016

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 777-REI
DP Barcode: D429902
Product Name: White

From: Ian Blackwell, Biologist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

Through: Karen Hicks, Team Leader
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To: Eric Miederhoff, PM 31
Regulatory Management Branch I
Antimicrobials Division (7510P)

Applicant: Reckitt Benckiser, LLC

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Alkyl dimethyl benzyl ammonium chloride	0.960
Octyl decyl dimethyl ammonium chloride, 40%	0.720
Didecyl dimethyl ammonium chloride, 24%	0.432
Dioctyl dimethyl ammonium chloride, 16%	0.288
Other Ingredient(s):	97.60
Total:	100.00

I BACKGROUND: Reckitt Benckiser, LLC, has submitted a set of acute toxicity studies in support of the data requirements of their new product, "White".

II RECOMMENDATIONS:

1. Each of the six studies is acceptable.

The acute toxicity profile for File Symbol 777-REI is currently:

Study	MRID Number	Toxicity Category	Study Status
Acute Oral Toxicity	49684507	IV	Acceptable
Acute Dermal Toxicity	49684508	IV	Acceptable
Acute Inhalation Toxicity	49684509	IV	Acceptable
Primary Eye Irritation	49684512	I	Acceptable
Primary Skin Irritation	49684510	III	Acceptable
Dermal Sensitization	49684511	**Sensitizer**	Acceptable

III LABELING: This labeling was determined by the OPP Label Review System.

PRODUCT ID #: 000777-00128

PRODUCT NAME: "White"

PRECAUTIONARY STATEMENTS

SIGNAL WORD: DANGER

Hazards to Humans and Domestic Animals:

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification. Child Resistant Packaging Required.

"Corrosive. Causes irreversible eye damage. Do not get in eyes or on clothing. Avoid contact with skin. Wear protective eyewear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals."

First Aid:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a Note to Physician which addresses the category I Primary Eye Irritant toxicity. The following statements are suggested types of information that may be included, if applicable:
- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Label Created by: Ian Blackwell on 01/27/2016 Last Updated by: Ian Blackwell on 01/27/2016

CRP and RUP statements

This product meets the Agency requirements for Restricted-Use Classification based on data that place it in toxicity category I for primary eye irritation. In lieu of assigning the product Restricted-Use classification, the product manager may consider alternatives such as face shield or goggles (to mitigate the identified hazards). Restricted-Use requirements vary depending upon use sites, e.g., institutional use, residential use, etc. Please refer to the 40 CFR §152.170 for information on Restricted-Use products.

Based upon data placing it in toxicity category I for primary eye irritation, this product meets the Agency requirements for Child-Resistant Packaging (CRP). However, the Agency does not require products that are assigned Restricted-Use status to be placed in CRP in addition to Restricted-Use Classification. CRP requirements vary depending upon use sites, e.g., institutional use, residential use, etc. Please refer to the 40 CFR, §157.22 and 157.24 for CRP requirements and exemptions. Thus, CTT recommends that the Product Manager assign this product Restricted-Use classification; if not, the registrant should place this product in CRP.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1, 870.1100)

Up and Down Procedure

Product Manager: 31 **Reviewer:** I. Blackwell
MRID No.: 49684507 **Study Completion Date:** 4/10/2015
Lab Study No.: 2014-00

Testing Laboratory: Product Safety Labs
Authors: Carolyn Lowe, LATG

Quality Assurance (40 CFR §160.12): Included

Test Material: Project White GLP Batch. "Blue liquid", pH 9-10.5

Species: Sprague-Dawley derived albino rat
Weight: 180-196 g **Age:** 9-11 weeks
Source: SAGE Labs

Conclusion:

1. LD_{50} (mg/kg):
Males= Not tested
Females= > 5,000 mg/kg
Combined= Not tested

2. The estimated LD_{50} is greater than 5,000 mg/kg of body weight.
3. Tox. Category: IV **Classification:** Acceptable

Procedure (Deviations from §81-1): None

Results:

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
5,000	---	1/4	---

Observations: Reduced fecal volume.

Gross Necropsy: Stomach and intestines extremely distended. Lungs dark red in color.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2, 870.1200)

Product Manager: 31 **Reviewer:** I. Blackwell
MRID No.: 49684508 **Study Completion Date:** 4/10/2015
Lab Study No.: 2014-0041

Testing Laboratory: Product Safety Labs
Author: Carolyn Lowe, LATG
Quality Assurance (40 CFR §160.12):

Test Material: Project White GLP Batch. "Blue liquid", pH 9-10.5

Species: Sprague-Dawley derived albino rat
Weight: Males= 251-293 g **Age:** 8-9 weeks
Females= 182-213 g
Source: SAGE Labs

Summary:

1. **LD_{50} (mg/kg):**
   Males > 5,000 mg/kg b.w.
   Females > 5,000 mg/kg b.w.
   Combined > 5,000 mg/kg b.w.

2. **The estimated LD_{50} is greater than 5,000 mg/kg of body weight.**

3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (Deviation From §81-2): None

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER DEATHS/NUMBER TESTED)		
	Males	Females	Combined
5,000	0/5	0/5	0/10

Observations: Blanching, erythema, edema, desquamation, eschar, superficial eschar, hyperkeratosis, anogenital staining.

Gross Necropsy Findings: The lab reported that there were no gross abnormalities.

DATA REVIEW FOR ACUTE INHALATION TOXICITY (§81-3, 870.1300)

Product Manager: 31
MRID No.: 49684509

Reviewer: I. Blackwell
Study Completion Date: 5/13/2015
Lab Study No.: 40085

Testing Laboratory: Product Safety Labs
Author: Carolyn Lowe, LATG

Quality Assurance (40 CFR §160.12): Included

Test Material: Project White - GLP Batch for Tox Testing Formula #e0042-153
Batch #: 2037-030; "blue liquid"; pH= 9.0-10.5
Concentration: gravimetric= 0.51, 2.41, 4.99 mg/L; nominal = 23.91 mg/L (nose-only)

Species: Sprague Dawley-derived albino rat
Weight: Males= 278-371 g Females= 189-238 g
Age: 8-9 weeks
Source: Sage Labs

Summary:

1. **LC_{50} (mg/L)** **Males=** 2.89 mg/L
Females= 2.41 < X < 4.99 mg/L
Combined= (cannot be determined)

2. **MMAD:** See Table below µm
4. **Toxicity Category:** IV **Classification:**

Procedure (Deviation From §81-3): None

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER DEATHS/NUMBER TESTED)		
	Males	Females	Combined
0.51	0/5	Not tested	0/5
2.41	2/5	0/5	2/10
4.99	4/5	4/5	8/10

Dose Level	MMAD	GSD
0.51 mg/L	2.31 µm	2.32 µm
2.41 mg/L	1.90 µm	2.01 µm
4.99 mg/L	2.18 µm	2.02 µm

Chamber Environment			
Exposure Concentration	0.51 mg/L	2.41 mg/L	4.99 mg/L
Chamber Volume	28 liters	28 liters	28 liters
Airflow	40 LPM	40 LPM	40 LPM
Temperature	20° C	20-23° C	22-23° C
Relative Humidity	30-31%	32-36%	47-51%

Clinical Observations: Rales, irregular respiration, gasping, hypoactivity, red facial staining, red nasal discharge, anogenital staining, abdominal distention, cold-to-touch.

Gross Necropsy Findings: Extremely red lungs; extremely to moderately distended stomach and intestines; light colored liver.

DATA REVIEW FOR *IN VITRO* EYE IRRITATION TESTING (§81-4, 870.2400)

Product Manager: 31 **Reviewer:** I. Blackwell
MRID No.: 49684512 **Study Completion Date:** 3/25/2015
MB Research Project No.: MB 14-23241.09

Testing Laboratory:	MB Research Labs
Study Authors:	Blair Yasso, B.S.
Test Method:	BOVINE CORNEAL OPACITY AND PERMEABILITY ASSAY (BCOP)
Study Title:	"Bovine Corneal Opacity and Permeability Test (BCOP-OECD)"

Quality Assurance (40 CFR §160.12): The report states the study was conducted in compliance with U.S. E.P.A. GLP Standards as published in the 40 CFR 160.

Test Material:	Project White – Cold Batch for Tox Testing Formula: e0042-153
Source of Eyes:	J.W. TREUTH & SONS, Inc.
pH of Test Material:	9.4 – 10.4
Dosage:	750 µL
Positive Control:	Ethanol
Mean Opacity Value:	69.34
Mean OD_{490} Value:	1.047
***In vitro* Score:**	85.05

Summary:

1. **Toxicity Category:** I

2. **Classification:** Acceptable

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: 31 **Reviewer:** I. Blackwell
MRID No.: 49684510 **Study Completion Date:** 3/17/2015
Lab Study No.: 40086

Testing Laboratory: Product Safety Labs
Study Director: Carolyn Lowe, LATG

Quality Assurance (40 CFR §160.12): Included

Test Material: Project White - GLP Batch for Tox Testing Formula #e0042-153
Batch #: 2037-030; "blue liquid"; pH= 9.0-10.5
Dosage: 0.5 mL

Species: New Zealand albino rat 3 females
Weight: 2824 – 3186 g **Age:** 12 weeks
Source: Robinson Services, Inc.

Summary:

1. **Toxicity Category:** III

2. **Classification:** Acceptable

Procedure (Deviations From §81-5): None

Results: One hour after exposure to the test material, each test subject displayed well-defined erythema and slight edema. Twenty-four hours after exposure, each test subject had moderate-to-severe erythema, moderate edema and blanching at the dose site. Forty-eight hours after exposure, each test subject had well-defined erythema, moderate edema and blanching. Seventy-two hours after exposure, 2/3 had well-defined erythema with moderate edema, 1/3 very slight erythema with slight edema. On Day 14 of the study, 3/3 subjects had very slight erythema, 1/3 very slight edema, 1/3 had desquamation and 3/3 had hyperkeratosis.

Special Comments: This study appeared to fall into acute toxicity category III. However, there was so much and long-lasting irritation, that we decided to check the PII of this product (which is rare for AD). The lab assigned this product a PII of 4.9. Had it been assigned 5.0, it would have been pushed into toxicity category II (2).

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: 31 **Reviewer:** I. Blackwell
MRID No.: 49684511 **Study Completion Date:** 3/17/2015
Lab Study No.: 40087

Testing Laboratory: Product Safety Labs (PSL)
Author: Carolyn Lowe, LATG

Quality Assurance (40 CFR §160.12):

Test Material: Project White - GLP Batch for Tox Testing Formula #e0042-153
Batch #: 2037-030; "blue liquid"; pH= 9.0-10.5
Positive Control Material: α-HexylCinnamAldehyde (HCA)

Species: Mouse, CBA/J
Weight: 17.1-20.3 g **Age:** 11-12 weeks
Source: The Jackson Laboratory

Method: Local Lymph Node Assay

Summary:

1. **This Product is a dermal sensitizer.**

2. **Classification:** Acceptable

Procedure (Deviation From §81-6): None

Procedure: The induction phase of the study began with PSL treating a test material group and a vehicle control group. There were five mice per group and the test material or control was applied for three consecutive days. Three days after the third induction treatment, PSL gave an IV injection of containing 20 μCi of ^{3}H-methyl thymidine. Five hours after the thymidine injections, the lab euthanized all of the animals and harvested each of the auricular lymph nodes and prepared them for a scintillation analysis.

Results:

Treatment Group	Mean DPM	Stimulation Index
Vehicle Control	2060.02	---
Positive Control	16550.01	8.03
100% Test Material	35857.41	17.41